Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 4, 6, 8 and 11 are pending in the application, with claims 1 and 8 being the independent claims. Claims 2, 3, 5, 7, 9 and 10 were previously canceled without prejudice to or disclaimer of the subject matter therein. Applicant reserves the right to pursue canceled subject matter in related divisional or continuation applications. Claim 1 has been amended to further clarify the language of the claim. As such, this change is believed to introduce no new matter, and its entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider the outstanding rejection and that it be withdrawn.

Applicant thanks the Examiner for withdrawing the prior rejection under 35 U.S.C. § 103(a) over Chandran *et al.* (U.S. Pat. No. 6,890,957 B2) in further view of Moeckel *et al.* (U.S. Pat. No. 5,955,106) and Ghebre-Sellassie *et al.* (U.S. Pat. No. 6,499,984 B1), and for apparently withdrawing the prior rejection under 35 U.S.C. § 102(b) over Timmins *et al.* (U.S. Pat. No. 6,031,004, hereinafter "Timmins *et al.*"). *See* Office Action at pages 2 and 3.

Rejection Under 35 U.S.C. § 103

In the Office Action at pages 3-7, the Examiner rejected claims 1, 4, 6, 8 and 11 under 35 U.S.C. § 103(a), as allegedly obvious over Timmins *et al.* in view of Langtry *et*

al. (*Drugs*. 1998; 55:563-584, abstract only, hereinafter "Langtry *et al.*"). Applicant respectfully traverses this rejection.

In proceedings before the U.S. Patent and Trademark Office (USPTO), the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 U.S.P.Q. 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Specifically, there must be a reason or suggestion in the cited art that would have prompted one of ordinary skill to combine the references, and that would also suggest a reasonable likelihood of success in making or using the invention as claimed as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Absent such reason or suggestion, the cited references may not be properly combined to render the claimed invention obvious. *See In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Furthermore, when references teach away there can be no expectation of success in combining the references. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* 72 Fed. Reg. 57526, at 57529, col. 3 (October 10, 2007)).

Timmins et al. do not teach formulations comprising metformin hydrochloride by itself, or that the most preferred metformin product is the hydrochloride salt.

In explaining the obviousness rejection, the Examiner alleges Timmins *et al.* teach a method for treating diabetes comprising administration of a metformin salt, such

as metformin hydrochloride, by itself or in combination with another oral antidiabetic agent, and teach that the "the most preferred metformin product is the hydrochloride salt." Office Action at pages 3 and 4. Applicant respectfully disagrees.

Timmins *et al.* discuss metformin salts of dibasic acids (in particular, metformin fumarate and metformin succinate) at a 2:1 molar ratio of metformin:dibasic acid. *See, e.g.*, col. 2, lines 44-51. Timmins *et al.* recite that metformin hydrochloride is concurrently marketed in the U.S. as Glucophage™. *See, e.g.*, col. 1, lines 15-17. However, Timmins *et al.* also recite:

> ... [f]ormulation of the metformin hydrochloride in a controlled release system is exceedingly difficult due, at least in part, to its extremely high water solubility.
>
> The currently marketed metformin hydrochloride salt has a pronounced saline, bitter taste. Accordingly, it is usually marketed as a coated tablet where the coating is designed to mask any unpleasant taste. However, where the metformin hydrochloride salt is in the form of scored-divisible tablets, it will not usually have a coating or outer layer to mask the unpleasant taste.
>
> Taste is of primary concern where the metformin hydrochloride is to be formulated as a chewable tablet or liquid indicated for children or adults who are not able to swallow tablets.
>
> In such cases, the unpleasant taste of the hydrochloride salt could lead to compliance problems.

Col. 2, lines 25-42. As such, Applicant respectfully disagrees that Timmins *et al.* teach formulations comprising metformin hydrochloride by itself, or that the most preferred metformin product is the hydrochloride salt. In fact, Timmins *et al.* teach away from formulations containing metformin hydrochloride by itself (and without metformin salts

of dibasic acids) because of the extremely high water solubility and the unpleasant, bitter taste of metformin hydrochloride. When references teach away there can be no expectation of success. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR,* 72 Fed. Reg. 57526, at 57529, col. 3 (October 10, 2007)). Thus, Timmins *et al.* cannot be used to support a *prima facie* case of obviousness of the claims.

Timmins et al. and Langtry et al. do not teach a solid pharmaceutical composition comprising the claimed combination of glimepiride and metformin hydrochloride.

The present claims recite a solid pharmaceutical composition comprising a synergistic combination of glimepiride and metformin hydrochloride, wherein the weight ratio of glimepiride and metformin hydrochloride is about 1/500 (claim 1), or a method of controlling blood glucose levels in a patient with type 2 diabetes, comprising administering to said patient a synergistic combination of glimepiride and metformin hydrochloride, in a solid dosage form, wherein the weight ratio of glimepiride and metformin hydrochloride is about 1/500 (claim 8). Timmins *et al.* do not teach a synergistic combination of glimepiride and metformin hydrochloride, and, as noted by the Examiner, do *not* teach a ratio of glimepiride and metformin hydrochloride of about 1/500 or the specific dose amounts of glimepiride and metformin hydrochloride of claims 6 and 11. *See* Office Action at page 4.

The Examiner relies on the disclosure of Langtry *et al.* to cure these deficiencies, asserting that Langtry *et al.* teach that the dosage of glimepiride is usually started at 1 mg/day titrated to glycemic control at 1-2 week intervals to a usual dosage range of 1-4 mg/day. *See* Office Action at page 5. Langtry *et al.* state that glimepiride stimulates

insulin release and may be combined with insulin treatment in patients with sulfonylurea failure. *See, e.g,* Abstract. However, Langtry *et al.* do not cure the deficiencies of Timmins *et al.* because Langtry *et al.* do not teach or suggest a combination of glimepiride and metformin, let alone a synergistic combination of glimepiride and metformin hydrochloride at a weight ratio of about 1/500.

The Examiner has not provided the requisite rationale for why the claimed invention would have been obvious over Timmins et al. in view of Langtry et al.

In explaining the obviousness rejection, the Examiner asserts that it would have been obvious to a person of skill in the art at the time the invention was made to manipulate the dose amount of metformin hydrochloride and glimepiride as taught by Timmins *et al.* based on patient parameters such as age, weight and severity of hyperglycemia. *See* Office Action at page 5. In addition, the Examiner asserts that one would have been motivated to combine these references because: (1) Timmins *et al.* teach formulations comprising metformin and a sulfonylurea (*e.g.*, glimepiride) for type 2 diabetes and Langtry *et al.* suggest that glimepiride may be used in combination with other antidiabetic agents to control glucose in doses of 1-6 mg; (2) the "individually known common utility" of the components of the references; and (3) it is routine in the medical and pharmaceutical arts to manipulate the weight ratios of active ingredients. *See* Office Action at pages 5-6. As such, the Examiner's rationale relies primarily on the assertion that a person of ordinary skill in the art would pick metformin hydrochloride from all available metformin salts, would pick glimepiride from all available sulfonylurea agents, and would then determine alternative dosages of metformin

hydrochloride and glimepiride to arrive at dosages within the claimed weight ratios, because such dosages were individually known.

A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *See* M.P.E.P. § 2143.01; *Ex parte Levengood,* 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993). "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR,* 82 U.S.P.Q.2d at 1396 quoting *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006). Furthermore, it is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection is based. *See* M.P.E.P. § 2144.03(a); *In re Zurko*, 258 F.3d 1379, 1385 (Fed. Cir. 2001). ("[T]he Board cannot simply reach conclusions based on its own understanding or experience-or on its assessment of what would be basic knowledge or common sense. Rather, the Board *must point to some concrete evidence* in the record in support of these findings." (emphasis added)). As the court held in *Zurko*, an assessment of basic knowledge and common sense that is not based on any evidence in the record lacks substantial evidence support. *Id.* In addition, the U.S. Supreme Court has held that "rejections on obviousness cannot be sustained by *mere conclusory statements*; instead, there must be some articulated reasoning with some rational underpinning to support the

legal conclusion of obviousness." *KSR,* 82 U.S.P.Q.2d at 1396 quoting *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006).

Applicant respectfully submits that the Examiner has not provided any "concrete evidence" in the record that one of ordinary skill in the art would arrive at a synergistic combination of glimepiride and metformin hydrochloride at a weight ratio of glimepiride and metformin of about 1/500, in view of the cited references. Rather, the Examiner has simply made an unsupported, conclusory statement that cannot and does not support a *prima facie* case of obviousness. *See KSR,* 127 S.Ct. at 1741. To combine references without evidentiary support constitutes impermissible hindsight. *See KSR,* 127 S. Ct. at 1740-41 ("A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art."). Applicant respectfully submits that the Examiner has used impermissible hindsight to arrive at the conclusion that the claims are obvious over Timmins *et al.* in view of Langtry *et al.* and has therefore not established a *prima facie* case of obviousness.

M.P.E.P. § 2141 provides exemplary rationales that may support a conclusion of obviousness. Of those, it appears that the Examiner may be alleging that the claimed subject matter was "obvious to try" because one of ordinary skill in the art could choose from a finite number of identified, predictable solutions in the art with a reasonable expectation of success. *See* M.P.E.P. § 2141(III)(E). Applicant respectfully disagrees that the claimed combination of glimepiride and metformin hydrochloride at a weight ratio of about 1/500 would be predictable, as detailed below.

For at least these reasons, Applicant submits that the Examiner has not established a *prima facie* case of obviousness over the cited references, and therefore respectfully requests that this rejection be withdrawn.

Even if prima facie obviousness were established, evidence of unexpected results exists which would overcome such a rejection.

Secondary considerations of non-obviousness include unexpected results, commercial success, long-felt need, failure of others, licensing by competitors, copying, initial skepticism and later praise by experts, and near simultaneous invention by others. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 694, 148 U.S.P.Q. 459, 467 (1966). The Federal Circuit has recently reaffirmed that the USPTO must in all cases consider any evidence presented by Appellants tending to support secondary considerations of non-obviousness. *In re John B. Sullivan and Findlay E. Russell*, 498 F.3d 1345, 84 U.S.P.Q.2d 1034 (Fed. Cir. 2007). As discussed above, the Examiner has not established a *prima facie* case of obviousness with respect to the claims. Moreover, the record demonstrates that *prima facie* obviousness, even if it were established, would be negated by the unexpected properties of the claimed invention, namely, the inventor's discovery of the claimed combination of glimepiride and metformin hydrochloride at a weight ratio of about 1/500.

Here, the Applicant has discovered that combinations of glimepiride and metformin hydrochloride at a weight ratio of about 1/500 have an unexpectedly improved effect on reducing blood glucose levels in diabetic patients. *See, e.g.,* paragraphs [0012], [0014] and [0033] of the specification as filed on July 26, 2004. As described in the specification, the treatment of patients with glimepiride and metformin

at a weight ratio of 1/500 resulted in unexpected decreases in glycosylated hemoglobin (HbA_{1C}), fasting plasma glucose levels, and prandial blood glucose levels compared to treatments with glimepiride and metformin alone. *See, e.g.,* paragraph [0033] of the specification. These data are reproduced in the table below, along with data from another study which measured the same parameters following treatment with metformin and glyburide (another sulfonylurea agent):

	Metformin 500 mg (present invention)	**Glimepiride 1 mg** (present invention)	**Metformin + Glimepiride 500 mg / 1mg** (present invention)	Metformin + Glyburide 1500 mg / 20 mg (U.S. Pat. No. 6,011,049)
Glycosylated Hemoglobin (HbA_{1c})	+0.06	+0.25	**-0.70**	+0.10
Fasting Plasma Glucose (FPG)	+0.75	+0.68	**-1.77**	+6.0
Prandial Blood Glucose	+1.08	+0.99	**-2.7**	*not determined*

Specifically, the above data show that combined treatment with glimepiride and metformin hydrochloride (1/500 weight ratio) resulted in a potentiated therapeutic efficacy that is unexpectedly greater than treatment with glimepiride or metformin alone. This potentiated effect was not observed with combined treatment of glyburide and metformin at significantly increased doses (20 times more sulfonylurea and three times more metformin). Thus, in view of the potentiated therapeutic efficacy observed only with glimepiride and metformin hydrochloride at a 1/500 weight ratio, the claimed combinations of glimepiride and metformin would not have been predictable. As such, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results would be sufficient to overcome such a rejection.

As further evidence in support of the non-obviousness of the claimed subject matter, Applicant submits herewith Exhibit A (González-Oritz *et al.*, *Rev. Inv. Clin.* 2004; 56:327-333; *see* paragraph [0012] of the specification). As explained in the Abstract (in English), Exhibit A provides data from a clinical study involving the treatment of diabetic patients with 4 mg of glimepiride alone, 2 g of metformin alone, or a combination of 4 mg of glimepiride and 2 g of metformin (1/500 weight ratio). The efficacy criteria evaluated in the study were either a decrease in glycosylated hemoglobin (HbA_{1C}, or "A1C" in Exhibit A) of 1% or more, or a reduction in A1C of 7% or less. According to the Abstract, the decrease in A1C concentration was -0.9 ± 1.6% in the glimepiride group, -0.7 ± 2.1% in the metformin group, and -1.3 ± 1.8 mg/dL in the combined therapy group. Thus, only the combination therapy group attained the efficacy criteria of decreased A1C of 1% of more. Furthermore, the percentage of patients attaining the efficacy criteria of 1% or more or a reduction in A1C of 7% or less was markedly enhanced in the combination therapy group compared to the monotherapy groups, while the frequency of adverse events was similar for all treatment groups.

Applicant also submits Exhibit B (González-Oritz *et al.*, *J. Diabetes Complications*, electronically published on October 10, 2008 ahead of print; copy of uncorrected proof provided) as additional evidence in support of non-obviousness. Exhibit B provides data from a clinical study comparing the efficacy of glycemic control in patients treated with 1 mg of glimepiride and 500 mg of metformin (1/500 weight ratio) to patients treated with 5 mg of glibenclamide (glyburide) and 500 mg of metformin. As detailed in Table 2, the percentage of patients who maintained glycemic control after 12 months of treatment, measured by A1C levels less than 7%, were

markedly higher in the glimepiride/metformin treatment groups compared to the glyburide/metformin treatment groups.

In sum, Exhibits A and B provide further support for the non-obviousness of the claimed subject matter because they provide evidence that the claimed combination of glimepiride and metformin unexpectedly met certain therapeutic efficacy criteria compared to monotherapy with glimepiride or metformin alone, or compared to combination therapy with metformin and another sulfonylurea agent. Therefore, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results would be sufficient to overcome such a rejection.

As such, for at least the above reasons, Applicant respectfully requests this rejection be withdrawn.

Conclusion

The stated ground of rejection has been properly traversed. Applicant therefore respectfully requests that the Examiner reconsider the presently outstanding rejection and that it be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Peter A. Jackman
Attorney for Applicant
Registration No. 45,986

Date: April 6, 2009

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

962268

Exhibit A

RIC

ARTÍCULO ORIGINAL

Eficacia y seguridad de la terapia hipoglucemiante oral combinada de glimepirida más metformina en una sola forma farmacéutica en pacientes con diabetes mellitus tipo 2 y falla secundaria a monoterapia con glibenclamida

Manuel González-Ortiz,* Esperanza Martínez-Abundis,*
Grupo para el Tratamiento de la Diabetes Mellitus con Combinaciones

* Unidad de Investigación Médica en Epidemiología Clínica, Hospital de Especialidades, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social. Guadalajara, Jal.

Efficacy and safety of glimepiride plus metformin in a single presentation, as combined therapy, in patients with type 2 diabetes mellitus and secondary failure to glibenclamide, as monotherapy

ABSTRACT

Objective. *To evaluate the efficacy and safety of glimepiride plus metformin in a single presentation, as combined therapy, in patients with type 2 diabetes mellitus (DM2) with secondary failure to glibenclamide.* ***Material and methods.*** *A randomized, double-blind, multicentric trial was carried out in 104 obese patients with DM2, fasting glucose >140 mg/dL and glycated hemoglobin A1c (A1C) > 8%, in spite of treatment with glibenclamide at maximum doses and medical nutrition therapy for at least the 3 months previous to the study. After randomization, the patients received in titrated way during 3 months one of the following treatments: up to 4 mg of glimepiride, 2 g of metformin or 4 mg of glimepiride plus 2 g of metformin in a single presentation. Efficacy criteria were either a decrease in A1C of 1% or more, or a reduction in A1C of 7% or less. Adverse events were carefully monitored during the study.* ***Results.*** *At the end of the study, the decrease in A1C concentration was -0.9 ± 1.6% (CI 95%: -0.2 to -1.5) in the glimepiride group, -0.7 ± 2.1% (CI 95%: 0.2 to -1.6) in the metformin group, and -1.3 ± 1.8 mg/dL (CI 95%: -0.6 to -1.9) in the combined therapy group. The percentage of patients that showed a decrese in A1C of 1% or higher was 35.1, 21.2 and 47.0% in the glimepiride, in the metformin and in the combined therapy groups, respectively (p < 0.001). The percentage of patients with decreased A1C of 7% or less was 18.9, 9.0 and 23.5% in the glimepiride, in the metformin and in the combined therapy groups, respectively (p = 0.01). The frequency of adverse events was similar for all the*

RESUMEN

Objetivo. Evaluar la eficacia y la seguridad de la terapia oral combinada de glimepirida más metformina en una sola forma farmacéutica en pacientes con diabetes mellitus tipo 2 (DM2) y falla secundaria a monoterapia con glibenclamida. **Material y métodos.** Se llevó a cabo un ensayo clínico multicéntrico, doble ciego, al azar, en 104 pacientes obesos, con DM2, que habían recibido monoterapia con glibenclamida a dosis máximas y terapia médica de nutrición durante al menos tres meses, y que presentaban glucosa de ayuno >140 mg/dL y hemoglobina glucosilada A1c (A1C) > 8%. Los pacientes recibieron durante tres meses en forma titulada hasta 4 mg de glimepirida, 2 g de metformina o 4 mg de glimepirida más 2 g de metformina en una sola presentación. Se consideraron como criterios de eficacia la disminución de 1% o más de A1C o su reducción a 7% o menos. Los efectos indeseables se vigilaron en cada visita. **Resultados.** Al final del estudio la disminución en la A1C en el grupo de glimepirida fue de -0.9 ± 1.6 (IC 95%: -0.2 a -1.5), en el de metformina de -0.7 ± 2.1% (IC 95%: 0.2 a -1.6) y en el de la combinación de -1.3 ± 1.8% (IC: -0.6 a -1.9). El porcentaje de pacientes que logró disminuir la A1C en 1% o más después del tratamiento fue 35.1, 21.2 y 47.0% para los grupos de glimepirida, metformina y combinación, respectivamente (p < 0.001). El porcentaje de pacientes que disminuyó la A1C a 7% o menos al final de la investigación fue 18.9, 9.0 y 23.5% para los grupos de glimepirida, metformina y combinación, respectivamente (p = 0.01). La frecuencia de efectos adversos fue similar en los tres grupos. **Conclusión.** La combinación de glimepirida más metformina en una sola forma farmacéutica durante tres meses fue eficaz y segura en pacientes con DM 2 y falla secundaria a monoterapia con glibenclamida.

groups. ***Conclusion.*** *The combined use of glimepiride plus metformin in a single presentation for 3 months showed to be efficacious and safe in patients with DM2 and secondary failure to glibenclamide.*

Key words. *Glimepiride. Metformin. Diabetes mellitus type 2 treatment. Oral antidiabetic drugs combined therapy.*

Palabras clave. Glimepirida. Metformina. Tratamiento para diabetes mellitus tipo 2. Combinaciones de antidiabéticos orales.

INTRODUCCIÓN

La enfermedad arterial coronaria es en la actualidad una de las principales causas de mortalidad en el adulto en la mayoría de los países industrializados, así como en algunos países de América Latina y en México.[1] El incremento de la cardiopatía isquémica en México se debe en gran parte a una elevada prevalencia de obesidad, diabetes mellitus tipo 2 (DM2), hipertensión arterial y dislipidemia; enfermedades que comparten como un mecanismo patogénico común al proceso de aterogénesis.[2] La DM2, en forma particular, incrementa la mortalidad general debido a que la mayoría de las estrategias encaminadas a mejorar su control fracasan por el inadecuado diagnóstico de la enfermedad y por la falta de adherencia a los regímenes terapéuticos indicados, lo que trae por consecuencia la aparición de complicaciones, disminución en la calidad de vida del paciente y un mayor gasto en los servicios de salud.[3]

Se ha establecido que muchas de las complicaciones crónicas de la DM2 tienen su origen en disturbios bioquímicos y celulares que anteceden a la aparición de las lesiones patológicas características en los tejidos afectados o de la enfermedad clínica manifiesta.[4,5] Evidencias experimentales vinculan a la hiperglucemia, que es el hallazgo patognomónico y cardinal de la diabetes, con las complicaciones. Dichas evidencias han mostrado que los regímenes intensivos para el control de la glucosa pueden disminuir el riesgo de aparición de las complicaciones, sin embargo, se ha observado que la implementación y el mantenimiento de tales regímenes son difíciles de llevar a cabo por la gran mayoría de los pacientes diabéticos.[6]

En los últimos años, numerosos agentes hipoglucemiantes orales se han desarrollado para tratar de incidir en los diferentes mecanismos y vías que conllevan a la DM2 y en la actualidad contamos con numerosas alternativas de tratamiento. De acuerdo con las recomendaciones generales para el control de la DM2, la terapia hipoglucemiante oral combinada es la elección a seguir en caso de una respuesta inadecuada a monoterapia.[7] Se menciona que un porcentaje variable de pacientes con diabetes requerirán de un segundo hipoglucemiante oral en algún momento dado de su vida. Existe evidencia que demuestra que la suma de un segundo agente antidiabético es efectiva para mejorar el control metabólico, sin embargo, no queda claro cuál sería el mejor fármaco a combinar.[8]

La falla secundaria observada en el grupo específico de las sulfonilureas se calcula que varía de 5 a 10% por año de uso, independientemente de la adherencia al tratamiento, la ganancia de peso y las enfermedades intercurrentes de los pacientes.[9] La literatura médica muestra que la terapia de combinación de alguna sulfonilurea más metformina ha logrado, en poblaciones de diferentes características, disminuir la concentración de hemoglobina glucosilada A1c (A1C) hasta en 2%.[10,11] Por otra parte, la combinación de una sulfonilurea más metformina va orientada a actuar sobre dos de los principales mecanismos fisiopatológicos de la diabetes mellitus tipo 2, que son la falla en la secreción de insulina y la resistencia periférica a dicha hormona,[12] por lo que la asociación sinérgica parece ser una buena alternativa terapéutica, principalmente para aquellos pacientes con hiperglucemia persistente.

El objetivo de la presente investigación fue evaluar la eficacia y la seguridad de la terapia hipoglucemiante oral combinada de glimepirida más metformina en una sola forma farmacéutica en pacientes con DM2 y falla secundaria a monoterapia con glibenclamida.

MATERIAL Y MÉTODOS

Se llevó a cabo un ensayo clínico multicéntrico, doble ciego, al azar, en 104 pacientes adultos (40 a 65 años) con DM2. Todos habían recibido monoterapia con glibenclamida a dosis máximas (20 mg/día) y terapia médica de nutrición de acuerdo a los criterios recomendados por la Asociación Americana de Diabetes[13] durante al menos tres meses y que presentaban glucosa de ayuno >140 mg/dL y A1C > 8%, por lo que se les consideró con falla secundaria a glibenclamida. Los pacientes firmaron la hoja de consentimiento informado, previa lectura y explicación por parte del investigador. El estudio reunió los

requisitos necesarios para realizar investigación en seres humanos y el proyecto fue previamente autorizado por los Comités de Investigación y Ética del Hospital de Especialidades del Centro Médico Nacional de Occidente del Instituto Mexicano del Seguro Social. Se incluyeron pacientes con índice de masa corporal (IMC) > 27 kg/m^2, con capacidad para la deglución y que hubieran dado su consentimiento voluntario por escrito. No se incluyeron pacientes con hiperglucemia grave (> 270 mg/dL), sospecha de embarazo, tratamiento con insulina, intolerancia o alergia conocidas a sulfonilureas o biguanidas, o con presencia de insuficiencia cardiaca, renal, cardiopatía isquémica, enfermedad vascular cerebral, neuropatía visceral, hepatopatía crónica o infección por el virus de la inmunodeficiencia humana. No se permitió la ingesta de medicamentos que presentaran interacción farmacológica con glimepirida o metformina, tales como acetazolamida, ácido nicotínico, ácido para amino salicílico, analgésicos antiinflamatorios no esteroideos, antagonistas 2 de histamina, barbitúricos, ciclofosfamida, clonidina, cloramfenicol, cumarínicos, disopiramida, epinefrina, estatinas, fenfluramina, fenotiacina, fibratos, fluoxetina, guanetidina, hormonas esteroides, ifosfamida, inhibidores de la monoaminooxidasa, laxantes, miconazol, quinolonas, reserpina, rifampicina, sulfamidas y tetraciclinas. Se consideraron como criterios de exclusión del estudio: presencia de hipoglucemia grave (< 60 mg/dL y la necesidad de ayuda de un tercero para su recuperación) aun con el empleo de las dosis mínimas, efectos indeseables intolerables, falta de adhesión al tratamiento médico (ingesta del medicamento < 80%), inasistencia a las visitas programadas (falta a la cita en >1 ocasión), enfermedad intercurrente o accidente que ameritara hospitalización, ingesta durante el estudio de medicamentos con interacción farmacológica con glimepirida o metformina y decisión de retiro voluntario. Se consideraron como criterios de eficacia la disminución de 1% o más de A1C o su reducción a 7% o menos.

Se realizó un periodo de lavado de una semana, donde a todos los pacientes se les suspendió la glibenclamida y se les hizo hincapié en seguir la terapia médica de nutrición a lo largo del estudio, donde las calorías se calcularon de acuerdo con su peso corporal con el propósito de llevar o mantener al paciente en el peso ideal. La adherencia a la terapia médica de nutrición se evaluó en cada cita programada a lo largo del estudio por medio de un recordatorio de alimentos de 24 horas. Se dio la indicación de continuar con la actividad física acostumbrada. Posterior al periodo de lavado, los pacientes fueron asignados al azar a alguno de los siguientes grupos de intervención farmacológica: glimepirida, metformina o la combinación de glimepirida más metformina. De acuerdo con la concentración de la glucemia basal la dosis fue prescrita de forma titulada como se señala a continuación: hasta 199 mg/dL los pacientes recibieron un comprimido de 2 mg de glimepirida o un comprimido de 1 g de metformina o un comprimido de 2 mg de glimepirida más 1 g de metformina en la misma presentación cada 24 horas; de 200 hasta 270 mg/dL recibieron 4 mg de glimepirida en dos comprimidos o 2 g de metformina en dos comprimidos o 4 mg de glimepirida más 2 g de metformina en la misma presentación en dos comprimidos, divididos en dos tomas al día. Los frascos contenedores de los medicamentos fueron idénticos y preparados por el laboratorio farmacéutico patrocinador con asignación de códigos, los cuales se conocieron hasta el final de la investigación. Durante el estudio, una persona sin conflicto de interés realizó el conteo de medicamento para la evaluación de apego al tratamiento.

Al inicio y 90 días después de la intervención farmacológica se investigaron el peso, la talla, se calculó el IMC con la fórmula: peso (kg)/[talla (m)]^2 y se determinaron las siguientes mediciones de laboratorio: glucemia de ayuno, A1C, insulina, colesterol total, colesterol de las lipoproteínas de alta densidad (C-HDL), triglicéridos, creatinina, ácido úrico, transaminasa glutámico oxalacética (TGO), transaminasa glutámico pirúvica (TGP) y deshidrogenasa láctica (DHL). A los 30 y 60 días del inicio del estudio se midieron la glucemia de ayuno, la A1C y la DHL.

Los efectos indeseables se registraron en cada visita en una hoja especial en donde se especificaron cada una de las manifestaciones clínicas que se consideraron como probables, posibles o directamente relacionadas con el uso de los fármacos ingeridos.

Se utilizaron técnicas enzimáticas (Ortho-clinical Diagnostics, Inc. Rochester, NY, USA) para las determinaciones de glucemia, colesterol total, C-HDL, triglicéridos, creatinina, ácido úrico, TGO, TGP y DHL, con coeficientes de variación intra e inter-ensayo menores al 3%. La A1C y la insulina fueron medidas por método enzimático de polarización fluorescente (Abbott Lab. Abbott Park. Il, USA), con coeficientes de variación intra e inter-ensayo menores de 5%.

ANÁLISIS ESTADÍSTICO

Para el cálculo del tamaño de la muestra se utilizó la fórmula correspondiente para ensayos clínicos,[14]

en la que se tomó en cuenta una confiabilidad de 95%, un poder estadístico del 80%, una desviación estándar de la hemoglobina A1C de 1.5% en población con diabetes mellitus tipo 2 y una diferencia esperada de 1.1% en la concentración de A1C, lo que dio por resultado 29 pacientes por grupo. Los resultados se reportan en promedio ± desviación estándar. Para el análisis de las variables cuantitativas se empleó la prueba de ANOVA y la t de Student. Para las variables cualitativas se utilizó la χ^2. Se calculó el intervalo de confianza al 95% (IC 95%). Se consideró un nivel de significación con una $p < 0.05$.

RESULTADOS

De los 104 pacientes, 51 fueron mujeres y 53 hombres. Las características clínicas y el perfil inicial de laboratorio fueron similares para los tres grupos de estudio (Cuadro 1). Después de los tres meses de la intervención, existió un incremento significativo del C-HDL después de la administración de glimepirida (Cuadro 1).

En la figura 1 se muestra la evolución de la glucosa a lo largo del estudio en los tres grupos de tratamiento, donde se encontró una tendencia a la dis-

Cuadro 1. Perfil clínico y de laboratorio inicial y 3 meses después de la intervención farmacológica.

	Glimepirida n = 37		Metformina n = 33		Combinación n = 34	
	Inicial	3 meses	Inicial	3 meses	Inicial	3 meses
Edad, años	53 ± 8		53 ± 7		53 ± 7	
Evolución, años	7 ± 4		7 ± 5		6 ± 4	
IMC, kg/m^2	29.9 ± 3.5	31.4 ± 8.5	31.3 ± 5.4	30.1 ± 4.2	31.3 ± 4.7	31.8 ± 5.0
Sistólica***	132 ± 17	126 ± 17	129 ± 15	119 ± 31	128 ± 9	128 ± 11
Diastólica***	79 ± 7	78 ± 9	80 ± 11	78 ± 8	81 ± 6	82 ± 6
Creatinina*	0.9 ± 0.3	0.8 ± 0.2	0.6 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	0.8 ± 0.3
Ácido úrico*	4.2 ± 0.8	4.5 ± 1.3	4.3 ± 1.2	4.3 ± 1.1	4.2 ± 0.8	4.3 ± 0.7
Colesterol*	191 ± 49	199 ± 46	219 ± 40	208 ± 32	206 ± 41	201 ± 37
C-HDL*	36 ± 10	43 ± 13****	40 ± 9	44 ± 24	43 ± 12	39 ± 11
Triglicéridos*	195 ± 117	184 ± 119	280 ± 231	208 ± 101	205 ± 102	232 ± 168
Insulina**	14.1 ± 8.3	12.1 ± 7.3	9.3 ± 2.9	9.1 ± 4.7	13.4 ± 7.0	13.1 ± 12.2
TGO, U/L	29 ± 18	34 ± 21	41 ± 16	37 ± 24	26 ± 15	33 ± 25
TGP, U/L	34 ± 26	34 ± 22	49 ± 26	42 ± 20	33 ± 22	31 ± 21
DHL, U/L	310 ± 167	336 ± 161	404 ± 181	352 ± 125	322 ± 156	323 ± 142

IMC: índice de masa corporal, C-HDL: colesterol de las lipoproteínas de alta densidad, TGO: transaminasa glutámico-oxalacética, TGO: transaminasa glutámico-pirúvica, DHL: deshidrogenasa láctica.
* mg/dL.
** µU/mL.
*** mm Hg.
**** p = 0.01 entre inicial y 3 meses en el grupo de glimepirida.

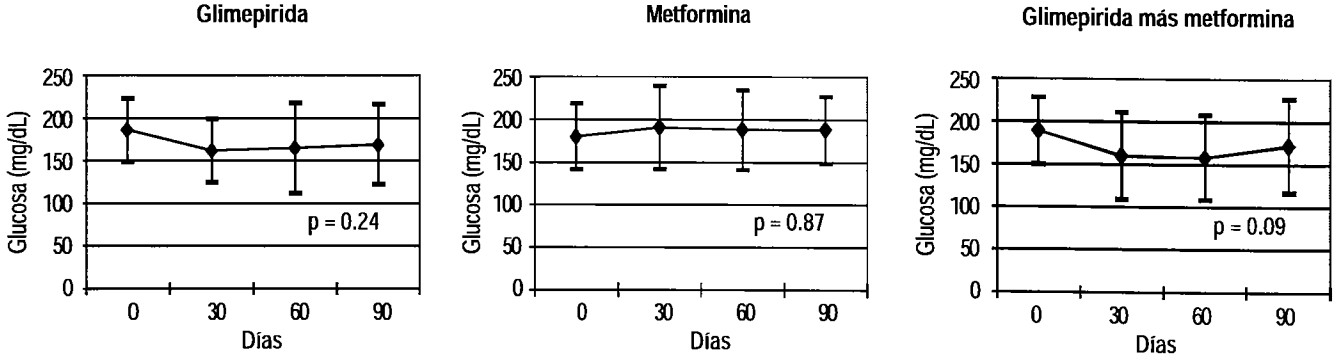

Figura 1. Concentraciones de glucosa a lo largo de los tres meses de tratamiento en los grupos de glimepirida (n = 37), metformina (n = 33) y combinación (n = 34). Prueba estadística: ANOVA.

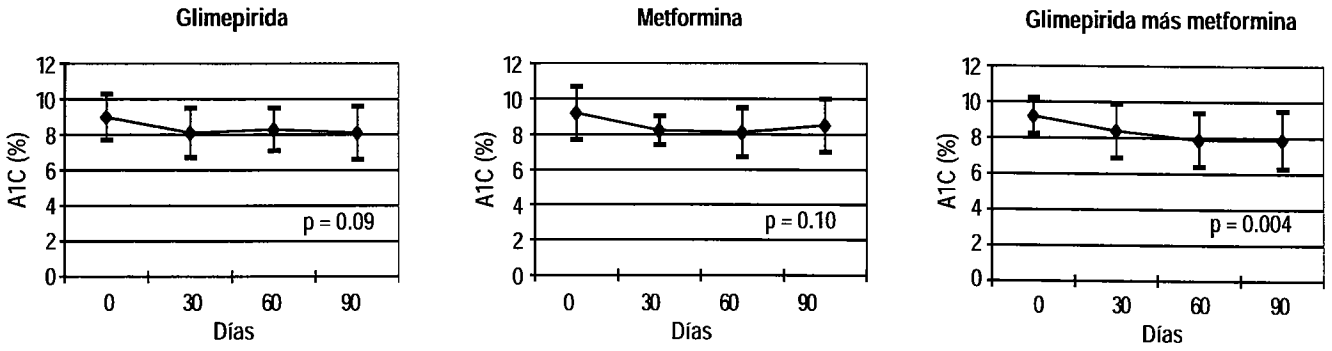

Figura 2. Concentraciones de hemoglobina A1C a lo largo de los tres meses de tratamiento en los grupos de glimepirida (n = 37), metformina (n = 33) y combinación (n = 34). Prueba estadística: ANOVA.

minución en los pacientes que recibieron la combinación de glimepirida más metformina. La disminución de la glucosa en el grupo de glimepirida después de los tres meses de tratamiento fue de -16.7 ± 57.5 mg/dL (IC 95%: 6.3 a -39.7), en el grupo que recibió metformina de 8 ± 48.6 mg/dL (IC 95%: 29.8 a -13.8) y en el de la combinación de -16.8 ± 58.8 mg/dL (IC 95%: 5.3 a -38.9).

Tal como lo muestra la figura 2, a lo largo del estudio existió una disminución significativa en la A1C en el grupo que recibió la combinación de glimepirida más metformina y una tendencia a su reducción en el grupo de glimepirida. La disminución de la A1C en el grupo de glimepirida después de los tres meses de tratamiento fue de -0.9 ± 1.6% (IC 95%: -0.2 a -1.5), en el grupo que recibió metformina de -0.7 ± 2.1% (IC 95%: 0.2 a -1.6) y en el de la combinación de -1.3 ± 1.8 mg/dL (IC 95%: -0.6 a -1.9).

El porcentaje de pacientes que logró disminuir la A1C en 1% o más después de tres meses de tratamiento fue 35.1 (n = 13), 21.2 (n = 7) y 47.0% (n = 16) para los grupos de glimepirida, metformina y combinación, respectivamente, con una diferencia estadísticamente significativa ($p < 0.001$) entre los grupos; que persistió entre glimepirida y metformina ($p = 0.02$) y entre la combinación y metformina ($p = 0.001$), pero no entre glimepirida y la combinación ($p = 0.08$).

El porcentaje de pacientes que logró disminuir la A1C a 7% o menos después de tres meses de tratamiento fue 18.9 (n = 7), 9.0 (n = 3) y 23.5% (n = 8) para los grupos de glimepirida, metformina y combinación, respectivamente, con una diferencia estadísticamente significativa ($p = 0.01$) entre los grupos; que persistió entre glimepirida y metformina ($p = 0.04$) y entre la combinación y metformina ($p = 0.004$), pero no entre glimepirida y la combinación ($p = 0.38$).

Los efectos indeseables consistieron principalmente en molestias gastrointestinales y fueron similares ($p = 0.50$) en los tres grupos [24.3% (n = 9) para glimepirida, 36.3% (n = 12) para metformina y 26.4% (n = 9) para la combinación]. La hipoglucemia se presentó sólo en 2.7% (n = 1) en el grupo de glimepirida, en el 3.0% (n = 1) en el grupo con metformina y en el 2.9% (n = 1) en el de la combinación y fue considerada como leve en todos los casos. En ningún paciente se requirió la suspensión del tratamiento por efectos indeseables o por alguno de los criterios de exclusión contemplados previamente en la metodología. No existió diferencia estadísticamente significativa entre los tres grupos ($p = 0.15$) en el porcentaje de pacientes que presentaron al final del estudio hiperglucemia grave (glucosa > 270 mg/dL) y que requirieron de alguna otra opción terapéutica para el control de su diabetes [35.2% (n = 13) en el grupo de glimepirida, 42.3% (n = 14) en el de metformina y 20.6% (n = 7) en el de la combinación de metformina más glimepirida].

DISCUSIÓN

Los resultados del Estudio Prospectivo de Diabetes en el Reino Unido (UKPDS) nos muestran que más de la mitad de los pacientes que tienen más de seis años de evolución de la diabetes requerirán en términos generales de la adición de un segundo agente hipoglucemiante oral para lograr el control de la glucosa.[9] En el presente estudio, los pacientes incluidos se encontraban en esa parte de la historia natural de la enfermedad, donde la monoterapia con glibenclamida no era suficiente para lograr las metas de control y, por ende, se requería de la adición de un segundo medicamento.

Son pocos los estudios que comparan directamente la efectividad de la combinación de agentes anti-

diabéticos, sin embargo, los resultados de diversas investigaciones en la literatura médica, con una de las combinaciones más utilizadas por su efectividad y seguridad, como es la de sulfonilureas con metformina, nos muestran que con esta estrategia se ha logrado disminuir la A1C hasta 2% en relación con la concentración previa al tratamiento.[8,10,11]

Para nuestro estudio elegimos como representante de las sulfonilureas a una de tercera generación, la glimepirida, que además de incrementar la secreción de insulina, presenta efectos extrapancreáticos relacionados con un incremento en las moléculas que facilitan el transporte activo de glucosa en el músculo y en los adipocitos, con el resultante incremento del ingreso de glucosa a la célula.[15,16] La metformina, medicamento considerado a combinar con la glimepirida, se reconoce como un antihiperglucemiante oral perteneciente a la familia de las biguanidas que potencializa los efectos metabólicos de la insulina en los tejidos periféricos e inhibe la gluconeogénesis hepática, además de reducir las concentraciones de triglicéridos y colesterol y propiciar la pérdida de peso.[17,18]

La experiencia clínica previa con el empleo de la combinación de glimepirida más metformina sólo ha sido publicada por Charpentier[19] en un grupo de pacientes con falla secundaria a la monoterapia con metformina. Cabe mencionar que en la evaluación de la efectividad de una segunda droga es importante tomar en cuenta la concentración basal de glucosa, ya que no se tiene una clara evidencia sobre cuál es el punto de corte de la glucemia en el cual se deba de indicar un segundo medicamento. En nuestro estudio, al igual que en el mencionado anteriormente, la glucosa basal de los pacientes antes de recibir la combinación fue similar, lo que facilita la comparación de algunos de sus resultados. En la investigación francesa, la disminución en la A1C fue de 0.7%, que es menor a la encontrada en nuestros pacientes después de recibir la combinación de glimepirida más metformina o la glimepirida sola y similar a la obtenida con la metformina sola. Esto nos permite corroborar la eficacia de la combinación en el manejo del paciente de difícil control, ya que logró disminuir la A1C al menos en 1% en cerca de la mitad de los pacientes, sin embargo, debemos reconocer que sólo un pequeño a moderado porcentaje de pacientes logró la reducción de la A1C por debajo de 7%. Desafortunadamente, en la presente investigación sólo se evaluó la glucemia de ayuno, en la cual sólo existió tendencia a la reducción en el grupo de la combinación y no fue evaluada la glucemia posprandial, que constituye uno de los puntos que recomienda la Asociación Americana de Diabetes para estimar el logro de las metas del tratamiento en el paciente diabético y cuya elevación, al igual que la hiperglucemia de ayuno, se asocian con un incremento en la A1C, sin embargo, con la reducción que se obtuvo en la muestra mexicana de A1C podemos presuponer una mejoría de la glucemia posprandial mayor que la publicada en la población francesa.[19] Cabe señalar, que otra limitante del estudio fue el corto periodo de manejo exclusivamente con dieta (una semana), aunque a los pacientes se les había prescrito terapia médica de nutrición al menos tres meses previos al estudio. Por otra parte, para la prescripción de las combinaciones se debe de tomar en cuenta las ventajas, desventajas y limitaciones de los medicamentos. En nuestra investigación, aproximadamente una tercera parte de los pacientes en los tres grupos requirió al final del estudio de la administración de insulina, al igual que en el grupo de Charpentier,[19] con lo que ratificamos el hecho de que no existe aún el medicamento ideal y de que la mayoría de los casos requerirán de una alternativa terapéutica adicional para alcanzar las metas de tratamiento.

Con excepción del C-HDL que aumentó en el grupo de glimepirida después del periodo de estudio, no se encontraron otros efectos metabólicos benéficos que se conocen de los dos fármacos utilizados, quizá debido al corto tiempo de la investigación o a las dosis empleadas.

Dentro de los efectos indeseables de la glimepirida se encuentran la hipoglucemia, los trastornos gastrointestinales y las reacciones alérgicas;[20] los reportados para la metformina son principalmente los gastrointestinales.[21] En nuestro estudio el porcentaje de los efectos adversos fue estadísticamente similar entre los tres brazos del estudio, lo que demuestra que esta combinación no presenta adición de los efectos indeseables de cada uno de sus componentes por separado. Por otra parte, debemos de señalar que ningún paciente requirió la suspensión del tratamiento debido a hipoglucemia y que existió buena adherencia al tratamiento.

En conclusión, la prescripción titulada de la combinación de glimepirida más metformina en una sola forma farmacéutica fue eficaz y segura en pacientes con DM2 y falla secundaria a monoterapia con glibenclamida, al disminuir la A1C después de tres meses de tratamiento y al ser bien tolerada durante el periodo de estudio.

AGRADECIMIENTOS

A Laboratorio Silanes, S.A. de C.V. por el financiamiento de este estudio.

NOMBRE Y AFILIACIÓN DE LOS INTEGRANTES DEL GRUPO PARA EL TRATAMIENTO DE LA DIABETES MELLITUS CON COMBINACIONES

Dr. en C. Manuel González Ortiz. Unidad de Investigación Médica en Epidemiología Clínica, IMSS. Guadalajara, Jalisco.

Dra. en C. Esperanza Martínez Abundis. Unidad de Investigación Médica en Epidemiología Clínica, IMSS. Guadalajara, Jalisco.

Dr. en C. Fernando Guerrero Romero. Unidad de Investigación Médica en Epidemiología Clínica, IMSS. Durango, Durango.

M. Esp. Cynthia Ávalos de la Cabada. Medicina Privada. Guadalajara, Jalisco.

M. en C. Rafael Bustos Saldaña. Unidad de Medicina Familiar 18, IMSS. Ciudad Guzmán, Jalisco.

M. en C. Fernando Grover Páez. Unidad de Medicina Familiar 39, IMSS. Guadalajara, Jalisco.

M. en C. José Antonio Robles Cervantes. Hospital General Regional 46, IMSS. Guadalajara, Jalisco.

M. en C. Martha Rodríguez Morán. Unidad de Investigación Médica en Epidemiología Clínica, IMSS. Durango, Durango.

M. en C. María Cristina Castellanos García. Unidad de Medicina Familiar 66, IMSS. Torreón, Coahuila.

M. Esp. Maricela Vidrio Velázquez. Hospital General de Zona 110, IMSS. Guadalajara, Jalisco.

M. Esp. Miguel Peniche Flores. Dirección Médica, Laboratorio Silanes, S.A. de C.V., México, D.F.

REFERENCIAS

1. Estadísticas de mortalidad en México: muertes registradas en el año 2000. *Sal Pub Mex* 2002; 44: 266-82.
2. Aguilar-Salinas CA, Vázquez-Chávez C, Gamboa-Marrufo R, García-Soto N, Ríos-González JJ, Holguín R, Vela S, Ruiz-Álvarez F, Mayagoitia S. Obesity, diabetes, hypertension, and tobacco consumption in an urban adult Mexican population. *Arch Med Res* 2001; 32: 446-53.
3. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. *Diabetes Care* 2002; 25: 1015-21.
4. Dandona P, Aljada A. A rational approach to pathogenesis and treatment of type 2 diabetes mellitus, insulin resistance, inflammation, and atherosclerosis. *Am J Cardiol* 2002; 90: 27G-33G.
5. Matthews DR. The natural history of diabetes-related complications: the UKPDS experience. United Kingdom Prospective Diabetes Study. *Diabetes Obes Metab* 1999; 1(Suppl. 2): S7-S13.
6. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321: 405-12.
7. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131: 281-303.
8. Lebovitz HE. Oral therapies for diabetic hyperglycemia. *Endocrinol Metab Clin North Am* 2001; 30: 909-33.
9. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. *Diabet Med* 1998; 15: 297-303.
10. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. UK Prospective Diabetes Study Group. *Diabetes Care* 1998; 21: 87-92.
11. Hermann LS, Schersten B, Bitzen PO, Kjellstrom T, Lindgarde F, Melander A. Therapeutic comparison of metfomin and sulfonylurea, alone and in various combinations. A double-blind controlled study. *Diabetes Care* 1994; 17: 1100-9.
12. Riddle M. Combining sulfonylureas and other oral agents. *Am J Med* 2000; 108(Suppl. 6A): 15S-22S.
13. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002; 25(Suppl. 1): S33-S49.
14. Jeyaseelan L, Rao PSS. Methods of determining sample sizes in clinical trials. *Indian Ped* 1989; 26: 115-21.
15. Muller G, Satoh Y, Geisen K. Extrapancreatic effects of sulfonylureas- a comparison between glimepiride and conventional sulfonylureas. *Diabetes Res Clin Pract* 1995; 28 (Suppl.): S115-S137.
16. McCall AL. Clinical review of glimepiride. *Expert Opin Pharmacother* 2001; 2: 699-713.
17. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med* 2002; 137: 25-33.
18. Wulffele MG, Kooy A, De Zeeuw D, Stehouwer CD, Gansevoort RT. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus; a systematic review. *Br J Clin Pharmacol* 2002; 53: 549P-550P.
19. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. *Diabet Med* 2001; 18: 828-34.
20. Schneider J. An overview of the safety and tolerance of glimepiride. *Horm Metab Res* 1996; 28: 413-18.
21. Howlett HC, Bailey CJ. A risk-benefit assessment of metformin in type 2 diabetes mellitus. *Drug Saf* 1999; 20: 489-503.

Reimpresos:

Dr. en C. Manuel González-Ortiz
Montes Urales 1409, Colonia Independencia,
44340, Guadalajara, México.
Tel.: +52 (33) 38267022. Fax: +52 (33) 36161218
Correo electrónico: uiec@prodigy.net.mx

Recibido el 25 de octubre de 2002.
Aceptado el 20 enero de 2004.

Exhibit B

ELSEVIER
Journal of Diabetes and Its Complications xx (2008) xxx–xxx
JOURNAL OF Diabetes AND ITS Complications
WWW.JDCJOURNAL.COM

Efficacy of glimepiride/metformin combination versus glibenclamide/metformin in patients with uncontrolled type 2 diabetes mellitus ☆

Manuel González-Ortiz[a,b,*], Jesús F. Guerrero-Romero, Rafael Violante-Ortiz, Niels Wacher-Rodarte, Esperanza Martínez-Abundis, Carlos Aguilar-Salinas, Sergio Islas-Andrade, Rosario Arechavaleta-Granell, Jorge González-Canudas, Martha Rodríguez-Morán, Etelvina Zavala-Suárez, Maria G. Ramos-Zavala, Roopa Metha, Cristina Revilla-Monsalve, Teresita J. Beltrán-Jaramillo

[a]*Medical Research Unit in Clinical Epidemiology, Specialties Hospital, Medical Unit of High Specialty, West National Medical Center, Mexican Institute of Social Security, Guadalajara, Mexico*
[b]*Cardiovascular Research Unit, Physiology Department, Health Sciences University Center, University of Guadalajara, Guadalajara, Mexico*

Received 22 February 2008; received in revised form 29 July 2008; accepted 13 September 2008

Abstract

Aim: The aim of this study was to compare the efficacy of glimepiride/metformin combination versus glibenclamide/metformin for reaching glycemic control in patients with uncontrolled type 2 diabetes mellitus. **Patients and Methods:** A randomized, double-blind, multicenter clinical trial was performed in 152 uncontrolled type 2 diabetic patients. Serum fasting and postprandial glucose, hemoglobin A1c (A1C), high-density lipoprotein cholesterol, and triglycerides were measured. After random allocation, all patients received two pills of glimepiride (1 mg)/metformin (500 mg) or glibenclamide (5 mg)/metformin (500 mg) po once a day. Dosage was increased to a maximum of four pills in order to reach the glycemic control goals (fasting glucose ≤7.2 mmol/l, postprandial glucose <10.0 mmol/l, A1C <7%, or an A1C ≥1% reduction). Statistical analyses were carried out using chi-square, ANOVA, or Student's *t* test. The protocol was approved by an ethics committee and met all requirements needed to perform research in human subjects; all patients gave written informed consent. **Results:** Each study group included 76 patients. No significant differences in basal clinical and laboratory characteristics between groups were found. At the end of the study, A1C concentration was significantly lower in the glimepiride/metformin group ($P=.025$). A higher proportion of patients from the glimepiride group (44.6% vs. 26.8%, $P<.05$) reached the goal of A1C <7% at 12 months of treatment. A higher proportion of hypoglycemic events were observed in the glibenclamide group (28.9% vs. 17.1%, $P<.047$). **Conclusion:** Glimepiride/metformin demonstrated being more efficacious than glibenclamide/metformin at reaching the glycemic control goals with less hypoglycemic events in patients with uncontrolled type 2 diabetes mellitus.

Keywords: Glimepiride; Glibenclamide; Metformin; Combinations; Metabolic control; Glycemic control goals

1. Introduction

Insulin resistance occurs early in type 2 diabetes disease process and may lead to progressive beta cell failure and overt diabetes (Abdul-Ghani, Tripathy, & DeFronzo, 2006). Monotherapy can slow down but does not prevent the progression of the disease. Successful management requires

☆ Financial source: Laboratorios Silanes, Mexico.

* Corresponding author. Montes Urales 1409, Col. Independencia, 44340, Guadalajara, Jalisco, México. Tel.: +52 33 38267022; fax: +52 33 36161218.
E-mail address: uicc@prodigy.net.mx (M. González-Ortiz).

1056-8727/08/$ – see front matter © 2008 Published by Elsevier Inc.
doi:10.1016/j.jdiacomp.2008.09.002

combination therapy that addresses both insulin resistance and beta cell dysfunction (Cefalu, Waldman, & Ryder, 2007). Clinical trials support the use of combinations of antidiabetic agents with complementary mechanisms of action such as a sulfonylurea/metformin (Dailey, 2003; Rendell, 2004). Early aggressive treatment could improve patient outcomes while reducing overall health care costs.

On one hand, glibenclamide/metformin is the oral antidiabetic combination most used in the clinical practice today (Dailey, 2003); on the other hand, glimepiride—considered as a third-generation sulfonylurea agent—has several beneficial pharmacological effects over glibenclamide, a second-generation sulfonylurea. Glimepiride combined with metformin in a single dose presentation has proved to be effective and safe for type 2 diabetes patients who fail with monotherapy on oral antidiabetic agents (González-Ortiz, Martínez-Abundis, & Grupo para el tratamiento de la diabetes mellitus con combinaciones, 2004).

At present, there is no evidence in medical literature of a comparison between the abovementioned combinations; therefore, the aim of this study was to compare the efficacy of glimepiride/metformin versus glibenclamide/metformin in reaching glycemic control in patients with uncontrolled type 2 diabetes mellitus.

2. Patients and methods

A total of 152 patients with type 2 diabetes mellitus (40 to 65 years of age) were included in a randomized, double-blind, multicenter clinical trial. Patients were overweight or obese [body mass index (BMI) between 25 and 40 kg/m^2] and had received monotherapy with metformin (2000 mg/day) and glibenclamide (20 mg/day) or medical nutritional therapy in accordance with the American Diabetes Association recommendations during at least 3 months. Patients were required to have fasting glucose concentrations of 8.3 to 14.9 mmol/l and hemoglobin A1c (A1C) >7%. Sample size was calculated with a clinical trial formula (Jeyaseelan & Rao, 1989) based on a confidence level of 95%, statistical power of 80%, standard deviation of A1C in uncontrolled type 2 diabetes patients of 1.30%, and an expected difference of 0.65% in A1C. Sample size was 63 patients per group, but it was increased to 76, estimating a 20% loss to follow-up.

Subjects were not included if they presented one of the following: pregnancy, alcohol or drug abuse, insulin treatment, allergy to sulfonylureas or biguanides, heart or renal failure (considered as serum creatinine >133 in males and >124 μmol/l in females), coronary heart disease, stroke, visceral neuropathy, cancer, systemic lupus, erythematosus lupus, or HIV infection. The use of drugs that presented pharmacological interactions with sulfonylureas or metformin was prohibited, with the exception of aspirin (≤100 mg/day).

The following were considered as exclusion criteria, but were statistically analyzed: mild or moderate hypoglycemia (>2 times); severe hypoglycemia (<3.3 mmol/l) with treatment at minimum doses; hyperglycemia >14.9 mmol/l with treatment at maximum dose during 3 months; severe adverse events; lack of compliance to medical treatment (<80% of prescribed pills were taken); loss of follow-up, >2 consecutive or 3 alternate visits during the study; hospitalization; unauthorized medication; or consent withdrawn.

The following clinical measurements were evaluated: BMI (weight in kilograms divided by height in meters squared), waist–hip ratio, blood pressure, fasting and postprandial glucose (glucose level 2 h after eating a standardized breakfast composed of 72 g of carbohydrates), A1C, high-density lipoprotein (HDL) cholesterol, and triglycerides. If a patient met all selection criteria, randomization was performed to include him or her in one of the following fixed combinations: two glimepiride (1 mg)/metformin (500 mg) pills (Glimetal 1/500, Laboratorios Silanes, Mexico) or two glibenclamide (5 mg)/metformin (500 mg) pills (Bi-Euglucon M5, Laboratorios Roche, Mexico), to be taken with breakfast as pharmacological intervention. The allocation was done by simple randomization by an independent center, and the sequence was concealed until the end of the statistical analyses. The medical nutritional therapy in accordance with the American Diabetes Association was followed throughout the study. If the patient presented an A1C >8% at 3, 6, or 9 months, the dose was doubled (two additional pills with dinner), reaching the maximum dose. In case of obtaining a fasting glucose <5 mmol/l every month, the dose was gradually decreased and the patient is closely observed for hypoglycemia through daily capillary glucose monitoring. Blind coded prescription containers were identical for both drugs. An independent researcher counted the pills in order to evaluate adherence to treatment.

Clinical measurements and fasting glucose levels were evaluated every month, postprandial glucose and A1C concentrations were evaluated every 3 months, and HDL cholesterol and triglyceride concentrations were evaluated every 6 months.

Adverse events were recorded continuously and classified as related or not related to the oral antidiabetic fixed combinations used in each case.

Efficacy criteria included fasting glucose ≤7.2 mmol/l, postprandial glucose <10.0 mmol/l, A1C <7%, or a reduction of A1C ≥1%.

Glucose, HDL cholesterol, and triglycerides were measured using an enzymatic technique (Abbott Laboratories, Abbott Park, IL, USA) with intra- and interassay coefficients of variation <3%. A1C concentrations were estimated using a fluorescent polarization enzymatic method (Abbott Laboratories) with intra- and interassay coefficients of variation <5%.

All subjects signed informed consents in order to participate in the study. The protocol was approved by an ethics committee and met all requirements to perform investigation on human subjects.

3. Statistical analysis

Numerical data were reported as mean and standard deviation, and nominal data were reported as proportion. The analysis was performed by intention to treat. A chi-square test was used in order to compare dichotomous variables. Student's *t* test was used to compare intra- and intergroup differences, and ANOVA test was used to evaluate changes throughout the study. A model of global multiple logistic regression was performed to adjust treatment efficacy (A1C <7 at 12 months) by basal BMI and A1C. *P* values <.05 were considered statistically significant.

4. Results

The glibenclamide/metformin group included 45 women and 31 men, and the glimepiride/metformin group included 48 women and 28 men (*P*=.410). There were no significant age differences between the glibenclamide and glimepiride groups (52.9±7.6 years vs. 52.3±7.6 years, *P*=.618).

BMI changes from the baseline to the end of the study were not significant between glibenclamide and glimepiride groups (0.7±1.5 vs. 0.4±1.7 kg/m^2, *P*=.254).

There was no significant difference between both groups in the time of evolution of diabetes (4.8±4.8 vs. 4.3±4.7 years, glibenclamide and glimepiride groups, respectively; *P*=.564).

There were no significant differences in clinical and laboratory characteristics between groups at baseline (Table 1).

There was no significant difference between the percentage of patients who increase the dose of drugs throughout the study at any time (for a total of 25% in glibenclamide group and 37% in the glimepiride; *P*=.451).

There were no significant differences between both groups in fasting and postprandial glucose levels throughout the study (data not shown). A significant difference in A1C concentration was observed at the end of the study, where A1C concentration was lower in the glimepiride group (7.6±1.2 vs. 7.2±1.0%, *P*=.025).

No differences were observed between glibenclamide/metformin and glimepiride/metformin groups regarding changes from baseline to the end of the study in fasting (−4.1±3.7 vs. −4.0±4.1 mmol/l, *P*=.945) and postprandial glucose (−4.3±5.3 vs. −4.2±4.6 mmol/l, *P*=.291) and A1C concentration (−2.0±1.5 vs. −2.1±1.6%, *P*=.712).

Table 1
Baseline characteristics

	Glibenclamide/ Metformin	Glimepiride/ Metformin	*P*
Systolic BP (mmHg)	124±12	124±17	.882
Diastolic BP (mmHg)	79±10	76±9	.054
BMI (kg/m^2)	29.6±4.3	29.5±4.1	.910
Waist–hip ratio	0.92±0.06	0.92±0.06	.864
Fasting glucose (mg/dl)	11.9±3.1	11.7±4.1	.645
Postprandial glucose (mg/dl)	17.5±4.6	16.8±5.2	.427
A1C (%)	9.6±1.6	9.4±1.8	.473
HDL cholesterol (mg/dl)	1.1±0.2	1.1±0.3	.519
Triglycerides (mg/dl)	2.8±2.3	2.6±1.7	.648

BP, blood pressure.

Table 2
Proportion reaching glycemic control goals

	Glibenclamide/ Metformin		Glimepiride/ Metformin	
	6 months	12 months	6 months	12 months
Fasting glucose ≤7.2 mmol/l	45.9	39.4	46.6	46.2
Postprandial glucose <10.0 mmol/l	29.7	18.3	27.4	21.9
Reduction in A1C ≥1%	78.4	76.1	75.3	67.7
A1C <7%	35.1	26.8	50.7	44.6 *

* *P*<.05 between both groups at 12 months.

Table 2 shows the metabolic control goals in both groups at 6 and 12 months; the glimepiride group showed the highest proportion of patients who reached the A1C <7% goal at 12 months of treatment.

The model of global multiple logistic regression to evaluate the efficacy of the treatment (A1C <7% at 12 months), adjusting for basal BMI and A1C, showed that the efficacy persisted in the glimepiride group (OR=2.170, 95% CI=0.034–4.559, *P*=.041), as well as after adjusting for basal A1C (OR=0.346, 95% CI=0.163–0.734, *P*=.006), observing an increased difference between both treatments, as basal A1C increases (A1C <9%: 46.4 vs. 51.7%; A1C ≥9%: 14.0 vs. 38.9%, glibenclamide and glimepiride groups, respectively).

The lipid profile remained without significant changes in both groups throughout the study.

Three patients in the glimepiride group were excluded for the following reasons: car accident, pancreatic cancer, and, in one case, having moved out of the country. Nevertheless, they were included in the statistical analysis. The adherence was 96% and 99% in the glimepiride and glibenclamide groups, respectively. Adverse events were present in 68.4% of patients in the glibenclamide group and in 69.7% of those in the glimepiride group (*P*=.842). The most common adverse events were upper respiratory infectious disease (27.7% in glibenclamide group vs. 28.9% in glimepiride group, *P*=.851) and sensorial abnormalities in lower extremities (28.9% in glibenclamide group vs. 35.5% in glimepiride group, *P*=.318). A higher number (*P*=.047) of mild and moderate hypoglycemic events was observed in the glibenclamide group (28.9%) in comparison to the glimepiride group (17.1%). No severe hypoglycemic events were present in any group.

5. Discussion

It has been clearly demonstrated that when the therapeutic treatment goals for diabetes are not reached, early progression to combination therapy can maintain

adequate control of blood glucose in comparison to that achieved with single-agent therapy (U.K. Prospective Diabetes Study Group, 1998). There are very few head-to-head studies that compare the effect between different combinations of antidiabetic agents. In the present study, two fixed metformin combinations were chosen: the first, with glibenclamide, a second-generation sulfonylurea, and the second, with glimepiride, a third-generation sulfonylurea that exhibits effects different from glibenclamide, including several extrapancreatic effects on muscle and adipose cells, elevating active glucose transport and increasing insulin secretion (Mûller, Satoh, & Geisen, 1995). There is no information about the comparison of the clinical effect of both sulfonylureas at specific doses; we used two common fixed combinations that could not be equivalent and which could be a limitation of our study. On the other hand, this investigation has methodological strength, obtained through controlling several variables by means of strict selection criteria, as a result of which both groups have similar clinical and laboratory basal characteristics, which did not have significant changes throughout the study. The medical nutritional therapy was permanently evaluated and modified in accordance to the individual characteristics of the patients; however, they did not receive specific indications to increase their physical activity, and this is another limitation of the study, independently of the probability of equilibrium of such characteristic in both groups due to the randomized design.

The first clinical experience with the glimepiride/metformin combination was published in a study wherein metformin failed as monotherapy; in the same study, a diminution of A1C of 0.7% was reached after 4 months of treatment (Charpentier, Fleury, Kabir, Vaur, & Halimi, 2001). On the other hand, we previously published the use of glimepiride/metformin in a single dose during a 3-month follow-up study, demonstrating its efficacy and safety in patients with type 2 diabetes with secondary failure to glibenclamide. In the abovementioned study, reduction of A1C was of 1.3% and approximately half of the patients showed an A1C reduction of at least 1%. Nevertheless, only a small percentage of patients reached the A1C goal of less than 7% (González-Ortiz et al., 2004).

In accordance with the new ADA-EASD guidelines, a sulfonylurea combined with metformin constitutes an attractive option in the clinical practice (American Diabetes Association, 2008). This combination can reduce A1C concentration up to 2% (Krentz & Bailey, 2005). Our results showed similar reductions in the fasting and postprandial glucose levels for both antidiabetic combinations used in the study, reductions that were evident from the first month of treatment. However, at the end of the study, A1C levels were significantly lower in the glimepiride group than in the glibenclamide group. These findings could be explained by the higher proportion of patients that reached the A1C goal of less than 7% in the glimepiride/metformin group. Besides, it is worth mentioning that A1C is a better parameter to identify metabolic control, because it evaluates the participation of both basal and postprandial glucose concentrations and their variability (Monnier, Colette, Dunseath, & Owens, 2007).

Although we waited for a lower rate of treatment adherence, this was high in both groups and was probably related to the close clinical attention provided by the medical staff.

Glibenclamide is well-known to induce a higher frequency of hypoglycemia than other agents, and our results were in accordance with this fact (Rendell, 2004). Other adverse events were considered to be not related to the combination of antidiabetic agents used, probably due to the natural evolution of diabetes.

In conclusion, glimepiride/metformin showed a greater efficacy in reaching the metabolic goal of glycemic control with less hypoglycemic events in patients with uncontrolled type 2 diabetes mellitus in comparison with glibenclamide/metformin.

References

Abdul-Ghani, M. A., Tripathy, D., & DeFronzo, R. A. (2006). Contribution of B-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care, 29*, 1130–1139.

American Diabetes Association (2008). Standards of medical care in diabetes—2008. *Diabetes Care, 31*, S12–S54.

Cefalu, W. T., Waldman, S., & Ryder, S. (2007). Pharmacotherapy for the treatment of patients with type 2 diabetes mellitus: Rationale and specific agents. *Clinical Pharmacology and Therapeutics, 81*, 636–649.

Charpentier, G., Fleury, F., Kabir, M., Vaur, L., & Halimi, S. (2001). Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. *Diabetic Medicine, 18*, 828–834.

Dailey, G. E. (2003). Glyburide/metformin tablets: A new therapeutic option for the management of type 2 diabetes. *Expert Opinion on Pharmacotherapy, 4*, 1417–1430.

González-Ortiz, M., & Martínez-Abundis, E., Grupo para el tratamiento de la diabetes mellitus con combinaciones. (2004). Eficacia y seguridad de la terapia hipoglucemiante oral combinada de glimepirida más metformina en una sola forma farmacéutica en pacientes con diabetes mellitus tipo 2 y falla secundaria a monoterapia con glibenclamida. *Revista de Investigacion Clinica, 56*, 327–333.

Jeyaseelan, L., & Rao, P. S. S. (1989). Methods of determining sample sizes in clinical trials. *Indian Pediatrics, 25*, 115–121.

Krentz, A. J., & Bailey, C. J. (2005). Oral antidiabetic agents: Current role in type 2 diabetes mellitus. *Drugs, 65*, 385–411.

Monnier, L., Colette, C., Dunseath, G. J., & Owens, D. R. (2007). The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care, 30*, 263–269.

Mûller, G., Satoh, Y., & Geisen, K. (1995). Extrapancreatic effects of sulfonylureas—A comparison between glimepiride and conventional sulfonylureas. *Diabetes Research and Clinical Practice, 28*(Suppl), S115–S137.

Rendell, M. (2004). The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs, 64*, 1339–1358.

U.K. Prospective Diabetes Study Group. (1998). UKPDS 28: A randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. *Diabetes Care, 21*, 87–92.